Modern Organic Chemistry Research, Vol. 1, No. 1, November 2016
https://dx.doi.org/10.22606/mocr.2016.11004

A Rapid and Green Procedure for the Synthesis of 5-Arylidene Rhodanine Derivatives

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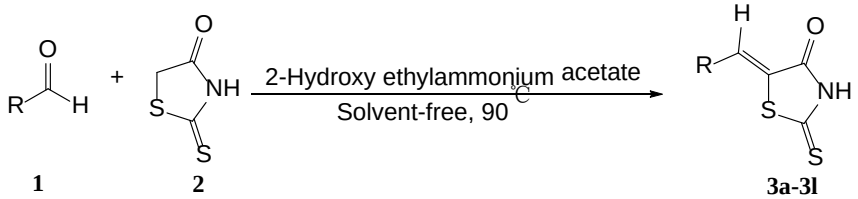
Abstract. A simple and efficient synthesis of 5-arylidene rhodanine derivatives by the Knoevenagel condensation of aromatic aldehydes with rhodanine in the presence of 2-hydroxy ethylammonium acetate under solvent-free conditions is described. The attractive features of this procedure are high yields, short reaction time, operational simplicity, mild and environmentally benign reaction conditions, easy preparation and reusability of the catalyst.

Keywords: 5-arylidene rhodanine derivatives; Knoevenagel condensation; solvent-free conditions; 2-hydroxy ethylammonium acetate

1 Introduction

Rhodanine derivatives have shown a wide range of pharmacological activities, which include anticonvulsant, antibacterial, antiviral, and antidiabetic effects [1-3]. The preparation of 5-arylidene rhodanine derivatives can be carried out by condensation of aromatic aldehydes and rhodanine in the presence of various catalysts such as glycine [4], ammonium acetate [5-6], 2,2,6,6-tetramethyl piperidine [7-8], NaOAc/HOAc [2,9-10], 1-butyl-3-methyl imidazolium hydroxide [11-12], NH_4Cl/NH_4OH [13], ethylenediammonium diacetate [14], $K_2CO_3/[bmim]BF_4/H_2O$ [15], piperidine [1,16-17], piperidine/AcOH [18-20]. Unfortunately, many of these methods suffer from one or other limitations such as low product yields, tedious work-up procedures, relatively long reaction time, use of organic solvent, use of special apparatus, use of expensive catalyst and difficulty in recovery and reusability of the catalyst. Thus, the development of an efficient and versatile method for the preparation of rhodanine derivatives is an active ongoing research area, and there is a potential for further improvement toward green chemistry and improved yields.

Organic reactions under solvent-free conditions have attracted much interest from chemists particularly from the viewpoint of green chemistry [21]. To the best of our knowledge, the activity of 2-hydroxy ethylammonium acetate for synthesis of 5-arylidene rhodanine derivatives has not been studied. Herein we report a rapid and green synthesis of 5-arylidene rhodanine derivatives via a condensation of aromatic aldehydes and rhodanine under solvent-free conditions using 2-hydroxy ethylammonium acetate as an efficient and recyclable catalyst (Scheme 1).



Scheme 1. Synthesis of 5-arylidene rhodanine derivatives

2 Experimental

2.1 General

All chemicals were commercial products. Melting points were determined on an X-4 micro melting point apparatus and were uncorrected. FT-IR spectra were obtained as KBr pellets on a Nexus 470 spectrophotometer. ^{1}H NMR spectra were recorded in deuterated dimethylsulfoxide on a Bruker Avance III 400 with TMS as internal standard.

2.2 Preparation of 2-hydroxyethylammonium Acetate

To aminoethanol (12.2 g, 0.2 mol) in a three-necked flask equipped with a reflux condenser and an addition funnel, acetic acid (12.0 g, 0.2 mol) was added dropwise with stirring. Stirring was continued for 24 h at room temperature, to give a yellowish viscous clear liquid (24.2 g, 100%). ^{1}H NMR (DMSO-d_6, 400MHz): δ 1.72 (s, 3H, CH_3–COO^-), 2.71 (t, 2H, –O–CH_2–), 3.48 (t, 2H, –CH_2–N), 6.55 (broad signal, 4H, –NH_3+OH).

2.3 General Procedure for the Synthesis of 5-arylidene Rhodanine Derivatives

A mixture of rhodanine (0.665 g, 5 mmol), the aldehyde (5 mmol), and 2-hydroxyethylammonium acetate (0.061g, 0.5 mmol) in a round bottom flask was stirred at 90 °C under neat conditions. The progress of the reaction was monitored by TLC (silica gel, using ethyl acetate-petroleum ether (1:1) as solvent). After completion of reaction, the reaction mixture was cooled to room temperature, whereupon it solidified. The solid mixture was recrystallized from ethanol to afford 5-arylidene rhodanine. All of the products are known, and physical data were found to be identical with those reported in the literature. The filtrate containing catalyst was subject to vacuum to remove solvent and the resulting catalyst was reused in four subsequent reactions without further purification.

3 Results and Discussion

2-Hydroxy ethylammonium acetate was easily prepared from cheaply available acetic acid and ethanolamine by a simple acid-base neutralization reaction [22]. In order to achieve optimum conditions, we initially investigated the reaction of 2,4-dichlorobenzaldehyde (5 mmol) and rhodanine (5 mmol) at different reaction temperatures (70, 80, 90 and 100 °C) in the presence of different amount of 2-hydroxy ethylammonium acetate (5% mol, 10% mol, 15% mol). The best result was obtained by carrying out the reaction with 10% mol of 2-hydroxy ethylammonium acetate at 90 °C under solvent-free conditions (Table 1).

Table 1. Effect of different reaction conditions on synthesis of 5-arylidene rhodanine [a].

Entry	Catalyst (mol%)	Temperature (°C)	Time (min)	Yield[b] (%)
1	10	70	60	62
2	10	80	14	81
3	10	90	11	84
4	10	100	11	84
5	5	90	11	67
6	15	90	11	83

[a] Reaction condition: 2,4-Dichlorobenzaldehyde (5 mmol), rhodanine (5 mmol), in the presence of 2-hydroxy ethylammonium acetate under solvent-free conditions.

[b] Isolated yield.

With this optimized procedure in hand, the generality of this reaction was examined using different aldehydes. As seen from Table 2, aromatic aldehydes having electron-donating as well as electron-

withdrawing groups were uniformly transformed into the corresponding 5-arylidene rhodanines in high to excellent yields within 2-11 min. Substituents on the aromatic ring had no obvious effect on yield or reaction time under the above optimal conditions. Arylmethylidenerhodanines can form two isomers. However, all arylmethylidenerhodanines reported in the present paper were obtained as single (Z)-isomers [3,13].

Table 2. 2-Hydroxy ethylammonium acetate catalyzed synthesis of 5-arylidene rhodanine derivatives [a].

Product	R	Time (min)	Yield[b] (%)	Mp (°C)	
				Found	Reported
3a	C_6H_5	2	94	204-206	205-207[15]
3b	4-$CH_3C_6H_4$	7	86	222-224	221-223[15]
3c	4-$CH_3OC_6H_4$	8	91	248-250	249-250[15]
3d	2-ClC_6H_4	3	81	179-181	181-182[15]
3e	4-FC_6H_4	2	93	218-220	219[3]
3f	4-$(CH_3)_2NC_6H_4$	3	91	269-271	270-271[15]
3g	4-BrC_6H_4	7	85	228-230	230[3]
3h	3-$NO_2C_6H_4$	5	95	262-264	263-265[15]
3i	4-ClC_6H_4	6	88	227-229	229-230[15]
3j	2,4-$Cl_2C_6H_3$	11	84	232-234	233-234[15]
3k	2-HOC_6H_4	10	82	222-224	221-222[10]
3l	2-Furyl	6	87	227-229	228-229[15]

[a] Reaction condition: aldehyde (5 mmol), rhodanine (5 mmol), 2-hydroxy ethylammonium acetate (0.5 mmol) at 90 °C under solvent-free conditions.

[b] Isolated yield.

The reusability of the catalyst was examined in the synthesis of 5-benzylidene rhodanine. The results were summarized in Table 3. When the reaction was completed, the reaction mixture was recrystallized from ethanol. The mother liquor was evaporated to dryness and the resulting catalyst was reused without any treatment [23]. It was found that the catalyst could be reused at least four times without significant loss of activity.

Table 3. Recycling of the 2-hydroxy ethylammonium acetate for the synthesis of 5-benzylidene rhodanine.

Run	Time (min)	Yield (%)
1	2	94
2	2	92
3	2	90
4	2	89
5	3	87

4 Conclusion

In summary, we have developed a rapid and environment-friendly method for the synthesis of 5-arylidene rhodanine derivatives by the condensation reaction of rhodanine and aromatic aldehydes in the presence of 2-hydroxy ethylammonium acetate. The present method has many obvious advantages, including simplicity of the methodology, ease of product isolation, good yields, short reaction time, use of a very cheap and recyclable catalyst, and being environmentally benign. We believe this will provide a practical alternative to the existing methods for the synthesis of 5-arylidene rhodanine derivatives.

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